NAMPT overexpression in prostate cancer and its contribution to tumor cell survival and stress response.

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Public Summary:
Nicotinamide phosphoribosyltransferase (NAMPT) is a rate-limiting enzyme in regenerating nicotinamide adenine dinucleotide (NAD(+)) from nicotinamide in mammals. NAMPT has crucial roles for many cellular functions by regulating NAD(+)-dependent SIRT1 deacetylase. However, roles of NAMPT in cancer are poorly defined. In this study, we show that NAMPT is prominently overexpressed in human prostate cancer cells along with SIRT1. Elevation of NAMPT expression occurs early for the prostate neoplasia. Inhibition of NAMPT significantly suppresses cell growth in culture, soft agar colony formation, cell invasion and growth of xenografted prostate cancer cells in mice. NAMPT knockdown sensitizes prostate cancer cells to oxidative stress caused by H(2)O(2) or chemotherapeutic treatment. Overexpression of NAMPT increases prostate cancer cell resistance to oxidative stress, which is partially blocked by SIRT1 knockdown. We demonstrate that in addition to modulating SIRT1 functions, the NAMPT inhibition reduces forkhead box, class 'O' (FOXO)3a protein expression and its downstream anti-oxidant genes catalase and manganese superoxide dismutase. Our results suggest important roles of concomitant upregulation of NAMPT and SIRT1 along with increased FOXO3a protein level for prostate carcinogenesis and their contribution to oxidative stress resistance of prostate cancer cells. These findings may have implications for exploring the NAMPT pathway for prostate cancer prevention and treatment.

Scientific Abstract:
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